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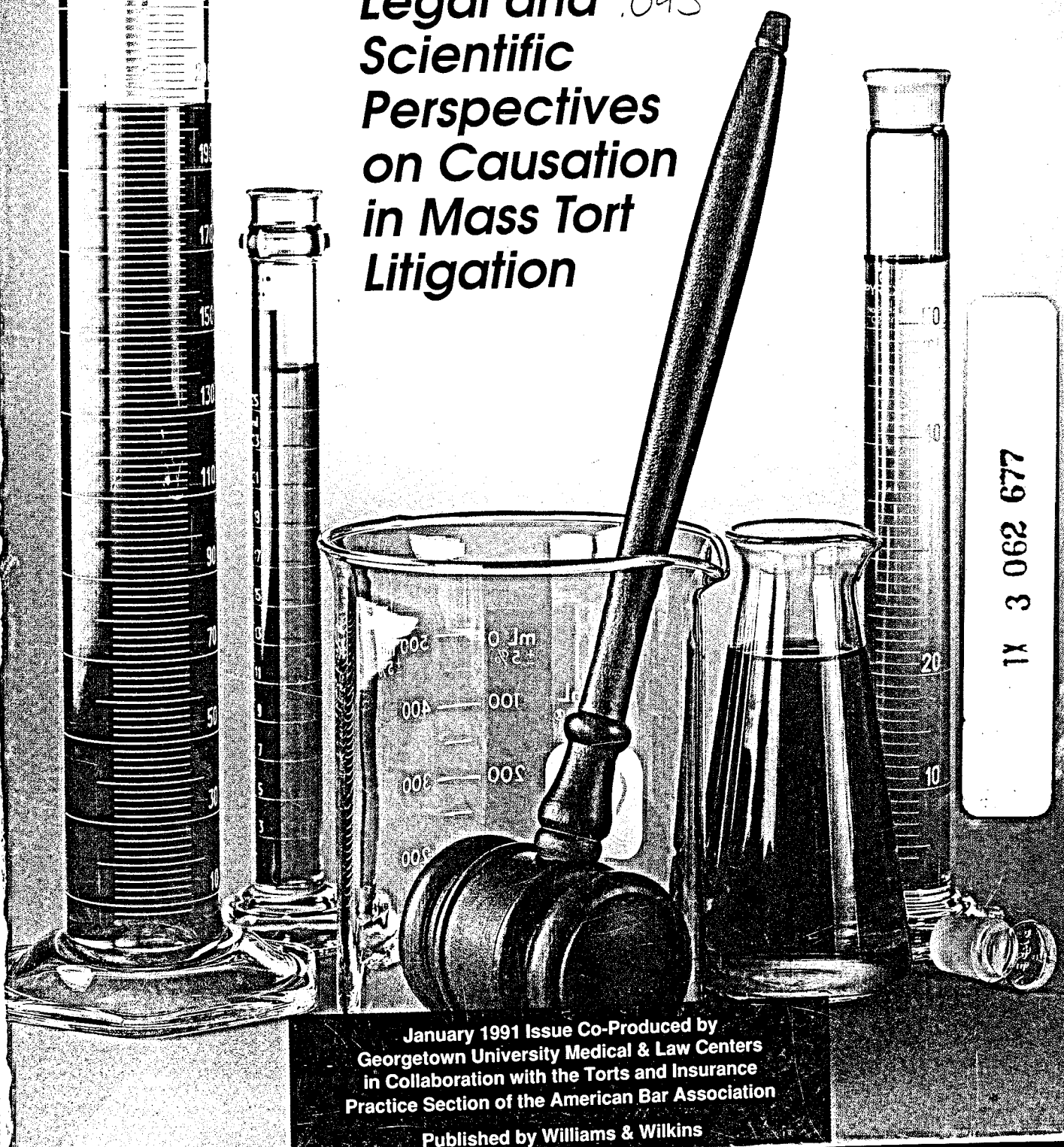

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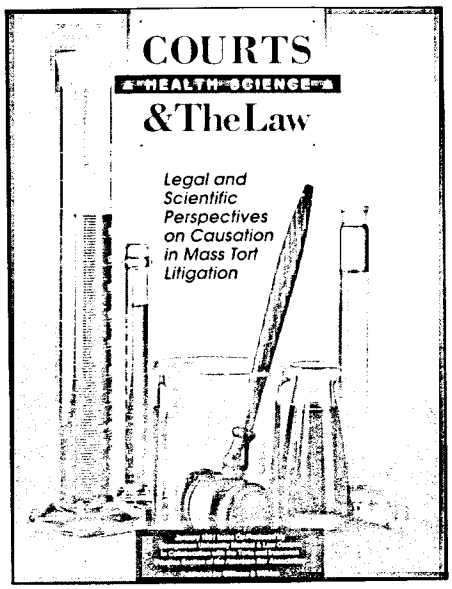

SYMPOSIUM

Legal and Scientific Perspectives on Causation in Mass Tort Litigation

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The Role of Toxicology in Causation

A Scientific Perspective

Ellen K. Silbergeld

"It is easy to consider human beings unique among living organisms. We alone have developed complicated languages that allow meaningful and complex interplay of ideas and emotions. Moreover, great civilizations have developed and changed our world's environment in ways inconceivable for any other form of life. Hence, there has always been a tendency to think that something special differentiates us from every other species.... This belief was first seriously questioned 125 years ago, when Charles Darwin and Alfred R. Wallace proposed their theories of evolution, based on the selection of the most fit.... An immediate consequence of the acceptance of Darwinian theory is the realization that life first existed on our Earth some four billion years ago in a simple form, possibly resembling the bacteria—the simplest variety of life known today. Of course, the very existence of such small bacteria tells us that the essence of the living state is found in very small organisms. Evolutionary theory further suggests that the same basic principles of life apply to all living forms" (Watson, Hopkins, Roberts, Steitz, & Weiner, 1987).

A fundamental tenet of late 20th century biology is that mechanistic explanations at the most basic level of biological organization do not lose their validity for explaining and predicting as molecular events are organized into cells, cells into organs, organs into organisms, and organisms into populations. The assumption of vertical integrity underlies the concentration of modern biology upon molecular and cellular phenomena; it has been reinforced by the many successes of modern biomedicine in understanding and treating disease on the basis of molecular theories of disease causation and prevention.

However, in law, resistance to the use of basic research has recently been expressed as an attack on these assumptions when used to establish causation. Causation is at the heart of scientific investigation, framed in either a retrospective or prospective hypothesis (what conditions preceded the present observation, or to what extent the present conditions permit prediction of future outcomes). The concept of causation in the law was historically developed by lawyers and philosophers in the absence of much discourse with scientists, so that it may not be surprising that vexing problems arise when the products and methods of science become relevant to legal decision making (Goldstein, 1989). A similar crisis of communication has been noted in the current contentions between neuroscientists and philosophers of knowledge (Churchland, 1988).

Among the vexing issues between scientists and lawyers, of relevance to this Symposium is the controversy over using scientific data and methods for establishing causation in toxic tort litigation. Among the arguments about causation in toxic torts, this paper will focus on those arising from the use of toxicological evidence in legal proceedings. There are other issues involved in causation, with their own problems of communication—for instance, determining exposure—but these will not be discussed here. Some of the discussion will be based upon two recent court decisions, *SOCMA v. Secretary, Department of Health and Human Services* (1989) and *In re: Paoli Railroad Yard PCB Litigation* (1980). In these two cases, there is judicial discussion of the role of toxicology in causation.

Toxicology is the study of biological responses of organisms, including humans, to endogenous and xenobiotic stressors. Toxicology can contribute to the understanding of disease that is not wholly determined by inheritance. Over the past decade, our understanding of diseases previously considered "idiopathic" (literally, self-caused) has identified the role of synthetic and natural toxins as causative agents (Office of Technology Assessment [OTA], 1990). This paper will deal with the preclinical or experimental body of data and the methods by which information is obtained on the likelihood that stressor substances are adverse to human health. Although experimental research concerns nonhuman subjects by definition, the sole purpose of such research is to increase knowledge related to human health. Among scientists as well as policy makers and lawyers, there is no reason for spending time and

resources to understand the effects of toxicants on rodents (for instance) as an end in itself. The large investment of public and private resources in experimental toxicology is based upon society's interest in understanding and preventing diseases with toxicant etiologies in humans. Thus, a rejection of the value of experimental data by those who make legal decisions is a challenge to the fundamental purpose of the endeavor and as such must be treated seriously by the profession of toxicology.

Recently, toxicology has become an important part of understanding causation in both law and medicine. A major reason for this is the continuing paucity of information on human responses to toxic substances derived from the direct study of exposed humans. Because of this, health decisions of many types are based upon experimental information. The alternative is acceptance of the occurrence of epidemic exposure and expression of observable disease or death in hundreds of people. The scale of our ignorance as to the potential toxicity of new and existing chemicals cannot be overestimated. Less than 20% of all chemicals currently on the TSCA inventory have any information as to their biological activities; of these, much less than 1% have data derived from observations on humans (Auer & Gould, 1987). This situation is not improving; as found by the U.S. General Accounting Office (GAO) in 1990, the record of the U.S. Environmental Protection Agency (EPA) in testing existing chemicals is getting worse (GAO, 1990). Given the obstacles to conducting definitive epidemiological studies (see below), the need to rely upon experimental data will continue. This situation is not unique to toxicology.

Second, more recent policy developments encourage reliance upon preclinical testing in many areas of decision making for the purpose of preventing damage to human health. Prevention cannot be accomplished by demanding data on humans which by definition can only be obtained after the event of damage.

Third, some types of information critical to understanding causation are not obtainable from human research. In many instances, these data are necessary to interpret the observations made on human subjects (see below; discussion of biological plausibility). The modern norms of research—the Nuremburg and Helsinki principles—particularly limit our ability to obtain data on human response to toxic chemicals, since deliberately exposing humans to such agents contravenes these ethical principles. The type of research undertaken by Kehoe in the 1930s on lead exposure is not permissible today.

Because of the essentiality of toxicology in understanding and preventing human disease, it is unreasonable and inefficient to exclude toxicology from legal decision making. It would separate causation as understood in medicine from causation as understood in law. The rejection of any and all toxicological data from legal decision making merely because it is derived from nonhuman organisms is scientifically unreasonable because of two powerful concepts in biology, Darwinism and cell theory, as noted in the introductory excerpt from a standard text in modern molecular biology and genetics. Exclusion of toxicological data is inefficient because it violates the principle of using the best data available, often the only data available. To refuse to consider toxicology would be to consider rational the decision by a mother to allow her child to drink a substance that had just killed her cat on the grounds that no human had yet been harmed by it. Unfortunately, that position is not too dissimilar from the position sometimes argued in the public arena today.

If these basic principles of rationality and efficiency are accepted—and it is recognized that they are not—it is important to develop consensus on the criteria for accepting toxicological data in reaching judgments about causation in a way that advances the purposes of law and policy without distorting the scientific base. It is important to develop objective criteria for using toxicological data in concert with other information related to causation as well as in the absence of other data. If there were in all cases sufficient human data, these issues would not be important. However, there are perceived differences between the results of toxicological and epidemiological studies, and these are often the source of the most contentious situations. How often these differences actually occur is not always carefully examined. I will discuss two examples of the use of toxicology in reaching decisions about causation in the absence of clear human data (dioxins and furans) and in the presence of considerable human data (lead). These examples are chosen because of my own experience in research and my involvement in regulatory and legal proceedings involving human exposure to these substances.

Causation in Toxicology: Basic Principles

It is a basic premise of this paper that many of the issues raised by using toxicology to establish causation are not different from the use of other types of scientific evidence—not surprisingly, since toxicology shares the general scientific method and assumptions about hypothesis testing and validation. Some of these issues will be discussed, but an in-depth analysis of scientific knowledge is beyond the scope of this paper.

Modern biology is based upon the holistic assumption that we do not differ from other species on the planet and that much of human biology is conserved through evolution. Studies on bacteria, yeast, fruit flies, nematodes, aplysia, chick embryos, sea urchins, squid, lobsters, mice, and rats have been the source of major advances in understanding human biology. This is not controversial. However, it seems that when such data are applied to the estimation of risk, it becomes acceptable in legal circles to reject

nonhuman species as predictive of human response. But a creationist approach to toxicology is a creationist approach to biology.

For instance, there is a high degree of homology among rats, mice, and humans in terms of the genetics of the major histocompatibility complex, a set of cell surface markers that can serve to define relatedness within and among species (Gill, Smith, Wissler, & Kunz, 1989). These similarities have allowed the use of rodents for developing organ transplantation techniques. The role of rodents in toxicology, particularly in studies of carcinogenesis and risk assessment, will increase: "with the increasing emphasis on genetic mechanisms in carcinogenesis, the availability of randomly bred, outbred, inbred, and congenic strains of rats will make this species even more useful in risk assessment" (Gill et al., 1989). A similar molecular argument has been advanced for the utility of fish as model systems in developmental biology and carcinogenesis (Powers, 1989).

Toxicology shares common aspects of hypothesis generation and testing in formulating causal arguments. A full discussion of the scientific method and its standards is beyond the scope of this paper [see Brush (1989) for a recent analysis of the theory of scientific knowledge]. Basic to science is the use of statistical methods to test hypotheses (Porter, 1987). Causation is defined in probabilistic terms by the relative exclusion of random associations among variables based upon statistically formulated and testable criteria. Objections to causal arguments in science as being "less than certain" because they are always probabilistic is an objection against science itself. All causation is basically probabilistic to the scientist, for two reasons: first, the inherent variability of matter and material phenomena, and second, the unavoidable imprecision of measurement. In this respect, the evidence of a tort involving a smoking gun and a corpse is not more deterministic (although it may be more probable) than evidence involving past employment in a lead smelter and kidney disease. The smoking gun, like Schrödinger's cat, is subject to the fundamentally probabilistic and quantum mechanical nature of the universe (Penrose, 1989).

Scientific knowledge also undergoes a test of plausibility, which Sagoff (1988) has compared to how well any new data fit the current "story" that scientists accept as the underlying explanation for the repertoire of events in the cellular arena in which the data are observed to occur. The reasonableness or plausibility of an explanation in science is tested by its consonance with other knowledge. This part of hypothesis testing is critically important in causality, beyond statistical testing, because statistics by themselves cannot establish direction or reasonableness. A current example of such plausibility testing is the way in which the "story" of bone physiology provides weight to relatively preliminary findings of increases in tumor incidence in animals exposed to fluoride (National Toxicology Program [NTP], 1990). Because of our general knowledge of the bone-seeking behavior of fluoride, the National Toxicology Program review panel gave added weight to the finding that fluoride-treated rodents have an increased incidence of osteosarcoma, a bone cancer.

Toxicology is similar to pharmacology, the study of the effects of specific agents on humans with relevance to the prevention and treatment of disease. (In the U.S., many toxicology programs are part of pharmacology departments.) In pharmacology, there is an additional criterion beyond statistical validity and biological plausibility that is often used in evaluating data and experimental design. This is the utility or direct relevance to human health and disease. Given the explicit function of pharmacology and toxicology to provide relevant information (often contrasted with the so-called "basic" sciences, in which understanding of process and event can be the primary objective of research), the results of research in these fields are considered meaningful insofar as they improve knowledge of human disease (cause, diagnosis, or treatment). The criterion of utility plays an important role in both experimental design and data interpretation. Toxicologists and pharmacologists choose designs that by experience have been most successful in predicting human response, and they interpret data on the basis of their relevance to human disease.

In the past, judgments of relevance were largely based upon empirical tests: that is, how well the results found in animals predict results in humans. Analyses of the extent of observed concordance have demonstrated the value of certain toxicological study designs, such as the carcinogenicity bioassay (Tomatis, Aitio, Wilburn, & Shuker, 1989). All known human carcinogens cause cancer in an experimental animal, and no known animal carcinogen is known to be noncarcinogenic in humans. Moreover, certain combinations of in vitro or short-term tests predict outcomes on long-term bioassays (Tennant et al., 1987). Under conditions where there is still considerable uncertainty as to basic mechanisms of action, these empirical analyses are important methods of demonstrating utility.

But relevance can be defined more rigorously than by calculations of concordance which are little more than ecological, to borrow a term from epidemiology to describe observations without an underlying hypothesis. The tools of molecular biology can provide compelling evidence for relevance, or the acceptability of extrapolations across species. One of the most complete studies of this type, of relevance to toxicology, has concerned the genetics of the P450 enzymes across species. These enzymes are involved in a number of responses to toxic substances. They are induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and by polychlorinated biphenyls (PCBs) (Safe, 1985; Silbergeld & Gasiewicz, 1989). Certain P450 enzymes activate procarcinogens such as benzo(a)pyrene (Gonzalez, 1989). Molecular biological studies have precisely defined the extent of evolutionary inheritance in gene

subfamilies between rats and humans over the past 800 million years of evolution, the location of specific genes on rat and human chromosomes, and the amino acid sequences of specific enzyme proteins in rats and humans (Gonzalez, 1989). From these studies, it can be shown that one of the major subfamilies of P450 genes present in all mammals is that which controls the activating enzymes for benzo(a)pyrene and the enzyme induction associated with TCDD. This provides justification for studying gene-toxicant interactions in mammals other than humans. Of course, other events in cellular regulation also govern gene expression and protein synthesis in species and individuals. This is the level at which future discussions about relevance should be conducted, instead of the current, often trivial, debate over such topics as comparative body surface size of rats and humans (see, for instance, Evans, Ozkaynak, & Wilson, 1982).

Another aspect of determining utility relates to dose, both route and amount. Ideally, experimental studies should examine the importance of route of exposure and, if this is important, model exposures by those routes of concern to human exposure. They should also examine dose-related responses and, to the extent possible, attempt to study effects within dose ranges that compare with those expected for humans. These ideal conditions are seldom possible to meet. Generally, it is assumed that exposures to toxicants in the environment are relatively low (this may not be true for all pesticides, food additives, or drugs deliberately administered). The route(s) of human exposure is usually determined by the point of release and the physical-chemical state of the substance. In most experimental studies, oral administration is utilized primarily for convenience and precision. As a matter of economy, studies on more complex routes of exposure (in terms of design and dosimetry), such as inhalation, are infrequently done. It is important to recognize that most human exposure situations involve more than one route of exposure: contaminants in drinking water may be volatilized and inhaled, and airborne contaminants may fall out onto surface water and dusts, from which they are ingested.

The matter of *amount* of exposure is more complicated. The evaluation of dosing in experimental studies requires judgment. Studies are obviously unacceptable if animals are treated with doses below those likely to be encountered by some humans. Evaluation of doses that exceed those estimated as likely for humans is more difficult. Because of the shorter life span of animals, the short duration of most "chronic" studies (28 to 90 days), and the insensitivity of detecting many types of effects in animals (such as neurotoxicity), toxicologists often design studies where dosage greatly exceeds the expected human dose. In carcinogenicity studies, a forcing condition known as the maximally tolerated dose has been incorporated into standard practice, and failure to obtain data from animals under maximally tolerated dose conditions is grounds for rejecting a study in the NTP. In reproductive toxicology, a criterion for evaluating dose is the maternal/fetal ratio (Fabro, Schull, & Brown, 1982). If the fetus is affected only at a dose larger than that associated with an effect in the mother (M/F > 1), it is assumed that it is more appropriate to evaluate the agent for its effects on the maternal (adult) organism.

A discussion of causation in toxicology would be incomplete without acknowledging the longstanding discussion within the field on the distinction between a so-called "biological effect" and a "toxicological effect" (Aldridge, 1986). Inherent in this distinction is the notion that substances can induce observable alterations in a biological parameter but that the alterations do not have any sort of deeper significance for the organism. The closer one examines this, however, the more difficult it becomes to determine what this means or how it would be proven. For a long time, this notion has been advanced to justify the assumption of thresholds, or a range of exposure that may induce responses but does not induce an effect. Biological explanations for this assumption have included the hypothesis that there are within organs an excess supply of cells or other functional reserve, or that within cells and organs there are mechanisms that produce perfect homeostatic compensation in the face of external perturbations.

With advances in knowledge, some of the simpler formulations of these assumptions have been discarded. Unfortunately, many standards are still based on erroneous concepts of so-called thresholds (Roach & Rappaport, 1990). Our ability to observe small events within cells and subcellular organelles has been greatly improved by such tools as electron microscopy, single cell recording, monoclonal antibodies, and DNA technology. Also, because of the general revolution in biology over the past 20 years, explanations for organ and organism level events are increasingly sought at the genetic level. What was once considered unimportant (or more often went unnoticed) is now understood to represent early events mechanistically involved in or increasing the probability of overt damage. In a larger context, the definition of a toxic effect largely depends upon what society is willing to tolerate in terms of health damage, as Needleman has noted in observing changing concepts of lead toxicity (Needleman, 1988).

Thus, it is increasingly difficult to make the old distinction between "adverse effects" and other types of response on the basis of science. It is now more generally accepted that most of the responses of organisms to toxic substances are on a continuum without clear qualitative bounds. It is more useful to consider all of the events consequent to exposure as biological markers, defined more by their operational use than by an inherent quality that they possess (NRC, 1987). For instance, the measurement of erythrocyte protoporphyrin, a protein synthesized in red

blood cells by enzymes affected by lead, has been used as a marker of lead exposure to identify at-risk persons. But elevated erythrocyte protoporphyrin is also a response of cells to the presence of lead. It thus denotes the occurrence of early events mechanistically related to lead-induced anemia and possibly neurotoxicity (EPA, 1986; Silbergeld, 1985).

In addition to its own internal debate about the nature of toxicological response, toxicology is also a victim of its own history. The famous statement by Paracelsus, "only the dose determines that a thing is not poisonous," can be easily misinterpreted to trivialize the whole field. Perhaps, after 450 years, this statement could be retired, particularly given its frequent misapplication as a justification for assuming that all toxicants have nontoxic doses. A more useful maxim to guide modern thinking comes from the 20th century toxicologist Browning: "There are no harmful substances; there are only harmless ways of using substances" (quoted by Aldridge, 1986). Paracelsus, an alchemist and homeopathic physician, emphasized the role of dose in defining an agent's properties; Browning emphasized the conditions of exposure; Aldridge (1986) has pointed to the equally critical role of sensitivity of outcome detection, as discussed above.

Another burden of history is toxicology's parentage in pathology, particularly in the German school. Pathologists have provided toxicologists with important tools to study organ system effects and to discern damage at the cellular and organelle levels (Fowler, 1987). However, despite the fact that Adrian Albert in 1954 first used the term "biochemical lesion" to describe devastating toxic effects involving interactions of toxicants with cellular biochemistry in the absence of visible damage, the inheritance of pathology has sometimes limited the range of toxicology to that which can be observed as morphological damage or measurable changes in cell numbers, size, or shape. This was for years a burden upon the field of teratology, where the term was restricted to conditions involving structural abnormalities induced in the organism in utero. Recognition of the effects of drugs and environmental agents on the fetal brain has caused toxicologists to include as teratogens substances that impact upon the functioning of the central nervous system without visible traces of damage (Rodier, 1978).

Resistance to Toxicology in the Law

As the pressure to reach closure on matters related to the identification and control of risks to human health has increased, relying upon toxicology has become controversial. Moreover, the explicit goal of prevention in environmental policy beginning with the Toxic Substances Control Act in 1976 has created a tension between prevention and remediation, or regulation and tort litigation, according to some scholars (Shavell, 1984). The focus of preventive environmental health since 1979 has been to prevent cancer, and in the decade since 1979, methods have been developed to expedite decision making in order to reduce human exposure to potential carcinogens. The emphasis on "potential" derives necessarily from the goal of prevention, because prevention requires action before data are available from humans. Waiting for the accumulation of data of human subjects is frequently an exercise in futility, given the limits and problems of epidemiological evidence (Davis, 1989; Karstadt, Bobal, & Selikoff, 1985).

Unfortunately, tort law has not been supportive of the goal of prevention, as tort actions are restricted to situations after the fact. Nevertheless, given the long latency between exposure and disease in many instances, tort law has an opportunity to play an important role in assisting preventive health policy by acting in the interval between exposure and disease. However, some lawyers and judges have objected to the admissibility or relevance of toxicology in this process. In two recent cases, these objections were stated in unusually strong terms. In *SOCMA v. Secretary, Department of Health and Human Services* (1989), the plaintiffs (a chemical industry trade group) sought to prevent publication by the National Toxicology Program (a part of the National Institutes of Health) of the *Fifth annual report on carcinogens*, a Congressionally mandated report by the National Institutes of Health, with respect to using experimental data to support findings that certain chemicals are "reasonably anticipated to be carcinogens" [42 USC S. 241 (b) (4) (A)]. In *Paoli Railroad Yard PCB Litigation*, defendants (the railroad and chemical companies) sought to exclude testimony by expert witnesses for the plaintiffs on the grounds that such testimony was based upon animal studies and as such were "totally irrelevant in a tort case." The U.S. District Court in Louisiana rejected the challenge to animal studies in *SOCMA*; the U.S. District Court in Pennsylvania agreed with the inadmissibility of animal studies in *Paoli*.

Although these cases are different in legal type, the basic goal of the government in *SOCMA* and the plaintiffs in *Paoli* was to prevent disease by acting early in the identification of a toxic hazard before irreversible damage or extensive exposure could take place. In both, toxicological evidence was an important basis for the case for preventive action. Yet the two decisions imply highly contradictory valuations of toxicology by the court: in *SOCMA*, that it is appropriate to base inferences as to the likelihood of human health effects ("anticipation") on experimental data in the absence of human data; in *Paoli*, that animal data have nothing to contribute to a determination of causation or disease, or risk of disease, in humans. There may be a rationale for requiring somewhat different criteria for causation in these two circumstances (Shavell, 1984), but it is hard to see how any rationale

could support such utterly different findings concerning the relevance of toxicology to etiological reasoning.

It might be understandable for the court to exclude toxicological data in cases where there are sufficient human data; in this case, it could be argued that toxicology is unnecessary (not that it is irrelevant); but this is not the case with PCBs (Safe, 1985). Alternatively, the court might be faced with a case in which toxicological data appear to conflict with well-established human data; but this is not the case with PCBs. As admitted by the court in *Paoli*, the existing human health database on PCBs is best described as inconclusive. Thus, in this instance as in many others, excluding toxicology has the effect of removing much of the scientifically relevant and useful information from consideration by the court. Deliberate rejection of relevant information violates good scientific practice.

The assertion of "total irrelevance" raises some concerns about the value given by law to science. Suspicions about science are prevalent in American society, although this is not to imply that such suspicions were necessarily present in *Paoli*. Nevertheless, antitoxicological attitudes can draw upon the deep-seated antiscientific feeling in the U.S. public associated with an unconvinced sentiment, described in the quotation from Watson. Antiscientific, antievolutionist sentiment still exists in the U.S., particularly in those with little training in biology. Coupled with a growing sympathy among the public for the extreme views of animal rights activists, there is the potential for a radical rejection of the holistic assumption of modern biology first stated by Darwin. When these views coincide with the interests of a powerful segment of society, as it can be argued they do, then it becomes difficult to separate legitimate from nonlegitimate objections to science in the courts.

There is a well-funded opposition to regulation and legal activity in the arena of responding to chemical risks to human health. This opposition seeks to clothe itself in the language of science, taking frequent refuge in invoking uncertainty and datagaps as reasons for inaction rather than prudence (Finkel & Evans, 1987; Silbergeld & Percival, 1987). The scientific culture of skepticism and allegiance to falsifiability (and an unbalanced fear of type 1 errors in statistical reasoning without appropriate apprehension for the dangers of type 2 errors) can make such advocacy appealing to scientists. This underlies appeals to "good science" by such industry advocacy groups as the American Industrial Health Council. When asked, scientists will usually agree that more research is always needed. In decision making, however, the definition of "sufficient information" is highly dependent upon the trans-scientific context of policy purpose and social value (Silbergeld, 1990).

Finally, there is an inconsistency in legal attitudes toward toxicology as compared to pharmacology. Toxicology may be compared to the unwelcome messenger, slain for bringing bad news. Probably because pharmacology brings "good news"—the hope of cures for dread disease or improvements in health and beauty—the claims of pharmacology are not often challenged, at their basis, for being fundamentally or totally irrelevant to human health, simply because they are based upon studies in nonhuman organisms. A recent instance of this dual standard can be seen in the claims made for a new pharmacological agent, MK-801, which, through its action at certain neurotransmitter receptors, is proposed to have utility to block stroke-related brain damage and other debilitating neurological conditions (cf. *New York Times*, November 22, 1989). There are no human data on MK-801, and some of its analogs, such as phencyclidine or "angel dust," give cause for caution as to its potential side effects. Yet a random walk through papers presented at the annual Society of Neuroscience meetings in 1988 and 1989 reveals no disclaimers as to the validity of inferring potential benefit to humans from relatively limited animal data. Because MK-801 is proposed to benefit human health, rather than to harm it, these relatively unfounded claims are accepted. To the scientist, it is somewhat alarming that the same data, if cited to infer the likelihood of risk, would probably be vilified for their assumption of predictability across species. Only suppose that MK-801 were a commercial chemical and the same claims were advanced by environmentalists (or plaintiff) as evidence of potential neurotoxicity!

The Need for Toxicology in Decisions Involving Causation

Efficiency

A goal of American law and public policy is to achieve societally agreed upon goals with a maximum of efficiency (Kelman, 1987). Although efficiency can be used as a shibboleth without regard for other goals of environmental and public health, such as civil liberties (Sagoff, 1988), it is still relevant to evaluate policy positions and methods of decision making in terms of efficiency.

Toxicology is clearly an efficient part of policy making in public health. The other option, exclusive reliance upon human data, is so inefficient that it would be immoral to insist upon it (Davis, 1988). The limits of epidemiology are compounded in environmental epidemiology, as compared to clinical trials, because of the vagueness of ascertainment and the need to rely upon natural experiments. A history of the accumulation of information on asbestos and cigarette smoking demonstrates that it is a long and slow process to obtain conclusive data on the causes of fatal disease. For other hazards, not associated with specific diseases or necessarily with death, the recognition of human health risk from epidemiological studies has been very long in coming. Waiting for "conclusive"

epidemiological evidence (which some still claim does not exist even for asbestos or cigarettes) results in the accumulation of considerable damage and imposes large costs on the exposed population. Because much chemical-induced disease is delayed in onset, there are institutional barriers preventing appropriate allocation to the source(s) of the hazard. Some of these are incorporated into law, such as limits on the time between "injury" and claim. Society pays these costs one way or another, inequitably and inefficiently, reflecting the inequities and inefficiencies of the American health system. Moreover, for chemically persistent hazards, such as lead or asbestos, successful delaying by parties liable for regulation or damage claims (or by government) results in further contamination of the environment. These materials do not disappear when the hazard is acknowledged and actions are finally taken to control sources. The billions of grams of lead used in gasoline from 1927 to 1984 in the U.S. remain as hazards in city streets, urban gardens, and school playgrounds (Agency for Toxic Substances and Disease Registry, 1988; Reagan & Silbergeld, 1990). Asbestos used as insulation remains a burden upon building owners and public managers to abate or control, with compounding of risks when improper abatement is undertaken (Davis & Mandula, 1985). In some instances, as with asbestos in schools, the public treasury is tapped to pay for the reduction of hazard accumulated during the long hiatus between the first evidence of hazard and actual action. The costs of abatement after delay tend to be greater because of more general contamination as well as the need to abate materials used after information on the hazard was available.

Prevention

As stated earlier, the major goal of public health policy is prevention of disease. Prevention of environmental and occupational disease requires identification of a hazard and institution of effective controls upon exposure. It is generally accepted that such primary prevention is more effective than diagnosis and treatment of disease after it begins. Moreover, in the American health care system, secondary prevention through early diagnosis and treatment does not always reach those most at risk. For instance, the poor rural black population of Triana, Alabama, exposed to DDT [dichlorodiphenyltrichloroethane] from an industrial discharger, was unlikely to have received medical care without the role played by the Centers for Disease Control (CDC) in detecting the exposure and the legal action that obtained a settlement from the company responsible (Kreiss et al., 1981).

Consistency of Regulatory and Tort Law

There is disagreement as to the appropriate degree of consistency between regulatory and tort law. From the scientific perspective, the same topics are addressed in both venues, and the same basic purpose is the underlying goal of decision making. Cranor (1989) has argued that regulatory and tort law related to toxic substances should be consistent in order to achieve justice. More mundanely, it is obvious that should one arena of redress conflict with the other, the public will pressure for change or seek redress exclusively in that arena most amenable to efficient transactions to accomplish its goals of compensation and punishment. The rise of the Superfund program can be seen as a response to the failure of tort law to constrain mismanagement of hazardous waste or to compensate victims of hazardous waste releases.

It may be argued that the purposes of regulation and tort law differ, that one is preventive and the other remediative (Shavell, 1984). It is not clear why differences in purpose should entail different concepts of causation such that, as stated in *Paoli*, evidence from animal studies is not at all admissible in tort cases while it is a major, often exclusive basis for regulation. The implications of *Paoli* may not be fully appreciated. In addition to establishing different criteria for prevention and remediation, it would allow industry to inflict considerable harm upon exposed populations with impunity prior to the reaching of a consensus finding on human health effects. It could also have the effect of permitting serial incidents of harm to occur in small groups of persons comprising cohorts of insufficient size for rigorous epidemiological analysis. This has happened frequently in the history of occupational medicine.

It has been argued that causal claims in tort law are different in kind from those in epidemiology or toxicology. Causal claims in tort law have historically avoided dealing with statistics because they are thought to rely on arguments about individual causation. However, the distinction between individual and aggregate causation, while of concern to law, is not particularly meaningful in a statistical sense given the assumption of statistics since the time of Bernoulli in the 18th century that, given large enough numbers, the probability of an event in an individual case is the same as the probability of the event in a large population [the "law of large numbers" (Porter, 1987)].

Cranor (1989) argues that similar principles of causation should govern regulatory law and tort law, despite differences in purpose. To Cranor's arguments it can be added that causal argument in regulation or prevention of injury must be consistent with that in tort law or remediation or injury. That is, setting a standard for vinyl chloride in air is a decision that implies, among other things, that exposures in excess of the standard are likely to injure health with a probability or severity deemed unacceptable (Corn, 1984). If this were not the case, regulation would be irrational and unrelated to public health. A further implication is that occurrence of exposures in excess of a scientifically based standard must be assumed to increase the probability of injury in exposed persons. If such persons manifest injury consistent with that found to be related to vinyl chloride in the process of

scientific review such as that during regulatory decision making, then it is a reasonable hypothesis that exposure in some manner caused or contributed to their injuries. This is not to ignore that there are other elements of causation in tort cases, such as defining the responsibility of the defendant or determining the actual exposure of the plaintiffs.

The Relationship between Epidemiology and Toxicology

If toxicology is rejected as a source of admissible information on causation, then only epidemiology remains for such purposes in law. It is sometimes argued that this decision is necessary because toxicological and epidemiological data are often inconsistent. There are four possible situations of consonance between toxicology and epidemiology: they may agree, they may be in dispute, there may be no information available from either field, or information may be available in only one. In the first case, where the findings of both fields agree, there should be little controversy, although a history of lead shows that disagreements persist in regulatory and tort law even in the face of remarkably consistent findings from experimental and clinical research (Needleman, 1988; Silbergeld, 1990). It is the two cases, where data are inconsistent or where there are no epidemiological data available, that problems appear to arise. These "confrontational" situations require careful examination before establishing criteria of exclusion across all cases. In many instances, the data from toxicology and epidemiology are not really inconsistent. In most cases, it is the case that different types of data are available, and these data are not clearly consistent in their findings. Thus, even in notorious circumstances, such as those related to TCDD (see below), it is not clear that the evidence of toxicology conflicts with that of epidemiology. A careful examination of the data from both fields reveals that the problem of integrating interpretation is more complex, a situation of datasets that are difficult to compare.

Setting epidemiology and toxicology in opposition tends to obscure how these fields are practically and theoretically interdependent. They are practically interdependent because epidemiology is frequently incomplete as to quantitative information on exposure. Toxicological data are important in understanding dose-response more precisely than is usually possible in epidemiological studies outside drug trials. The internal validity of experimental research is usually greater than that of epidemiological research. Theoretically, rejecting toxicology makes it difficult to construct causal inferences from epidemiological data. Toxicology provides the data for satisfying the criterion of biological plausibility, identified by Hill and Evans as one of the critical elements of epidemiological reasoning (Evans, 1976). The criterion of biological plausibility, discussed above, is met by evaluating the findings of a study in the context of preexisting knowledge of the biology of target organs and physiological systems. Almost always, this means consulting experimental or basic research. As noted above, the "goodness of fit" of an observation with the overall "story" of biology is part of the process of mechanistic toxicology, an endeavor not practicable in human subjects because of the inaccessibility of target sites of action within organs and cells. Without knowledge of mechanisms, even the best epidemiological study is basically hypothesis generating.

Notions of cause in science involve knowledge of mechanism. They go beyond the accumulation of linked observations, although this accumulation can stimulate the search for novel mechanisms. For instance, knowledge about the neurobiology of excitotoxic amino acids was utilized to develop hypotheses and design epidemiological studies on the possible association between diet and dementing disorders in Guam (Spencer et al., 1987). Animal studies in well-validated mechanists models are routinely used to predict potential effects of new drugs. For example, such studies on bromocryptine and other ergots preceded their application in clinical trials as treatments for parkinsonism (Fuxe & Calne, 1979).

Currently, there is a concerted effort to identify and validate more rapid and preferably in vitro predictive models, based upon mechanistic understanding, in order to speed up data acquisition and reduce the use of animals in both toxicity and efficacy testing (OTA, 1986). It should be a matter of some concern that advances in in vitro methods might be subject to even more suspicion than the results of in vivo methods in current use. There is little purpose to replacing whole animals with cell culture or tissue systems if the results are to be judged as even more totally irrelevant to predicting beneficial or adverse effects in humans.

Mechanistic research has been important to understanding several classes of toxicants, such as organophosphate pesticides and hexacarbon solvents (OTA, 1990). The development of so-called physiologically based pharmacokinetic models (NRC, 1986) and the whole process of carcinogen risk assessment (Perera & Boffetta, 1988) are based upon mechanistic research. Extrapolation of dose-response outside the range of observation is based upon mechanistic inferences. Even greatly increased investments in carcinogenesis bioassays, an investment searchingly questioned by Lave & Omenn (1986), would not resolve this problem. As they argue, it is more useful to increase the use of short-term animal studies targeted to elucidate specific mechanisms of carcinogenicity rather than to invest resources in very expensive epidemiological studies or expensive lifetime cancer bioassays for all chemicals.

To evaluate toxicology and epidemiology as epistemological adversaries to determine which source of

evidence to admit and which to exclude thus obviates the ways in which these two disciplines can complement each other. Two examples are given below.

Lead

Among environmental toxicants, lead has the largest body of data derived from studies of exposed humans. This is because of the long history of human intoxication by lead, going back over 2,000 years in medical history. The many uses of lead and its long history of human exploitation have resulted in many populations with significant exposures in occupational and nonoccupational settings (Wedeen, 1984). Experimental research on lead, specifically on lead neurotoxicity, began in 1968, more than 200 years after the description of human lead neuropathy by Tanquerel des Planches in 1738.

The clinical studies on lead toxicity by themselves are sufficient to derive remarkable strong estimates of human risk (Needleman & Gatsonis, 1990). These studies report adverse health effects down to exposures well within those found commonly in nonoccupationally exposed populations in the U.S. However, the clinical studies cannot answer two critical questions about lead as a neurotoxin: Is there a threshold for lead effects, and why is lead so potent a neurotoxin for young children? For these, research in animal models has been essential. The studies on fundamental mechanisms of lead toxicity have identified lead-calcium interactions as the likely basis for neurotoxicity (Silbergeld, 1985). Experimental studies also provide reasons to understand why lead effects are devastating for the young: first, the timing of lead exposure with brain development may produce effects that cannot be reversed after that developmental stage is passed; second, removing lead from brain is extremely difficult. Experimental research has found that lead appears to be able to enter into the endocrinological system that responds to and controls calcium in the body. This may explain how lead is absorbed and distributed in the body, its particular affinity for the developing nervous system, its transfer from mother to fetus, and its localization within cells.

TCDD

TCDD remains one of the most contested subjects in law and regulation. It is widely claimed to be an instance of irreconcilable conflict between epidemiological and toxicological data (Finkel, 1988). On that basis, several commentators have called for a general rejection of the assumption of congruity between experimental and human biology (e.g., Ames and Whelan). It is important to determine whether a real conflict exists between the data from epidemiology and toxicology. As reviewed recently, these datasets are not in clear conflict (Silbergeld & Gasiewicz, 1989). Two panels of experts, reviewing the available data in 1989, determined that the epidemiological data are inconclusive (NRC, 1989; Science Advisory Board, EPA, 1989). The issue of carcinogenicity, demonstrated in animals, has not been unquestionably excluded in humans. Some reports of occupationally exposed cohorts indicate no apparent excess incidence of cancer overall or on a site-specific basis, whereas other reports—particularly of cohorts exposed accidentally in Japan and Italy to dioxins and dibenzofurans—indicate increases in certain cancers. The larger studies of Vietnam veterans and workers in the U.S. being conducted by CDC remain highly controversial, particularly in terms of completeness and exposure assessment (Zumwalt, 1990).

The reproductive toxicity of TCDD is even less clear in human populations (Silbergeld & Mattison, 1987). In this case, the data from toxicology are not so much in conflict as they are unequal in type and weight. Very few studies of humans exposed in well-defined circumstances have been undertaken; in many studies, the relative importance of male- versus female-mediated effects cannot be distinguished (for instance, the spraying studies). The large registry study done by CDC, while yielding some apparent associations between Vietnam service and excess incidence of birth defects and childhood cancer, is difficult to interpret. The best-defined study of the Yucheng population in Taiwan exposed to dibenzofurans in cooking oil has found evidence of persistent transplacental toxicity and developmental toxicity in children born to women during and after the time of active exposure (Rogan et al., 1988). Some of the effects observed in children (neurotoxicity) have not been studied in animals.

The experimental data on TCDD are quite useful when used in consonance with the available human data for developing science-based approaches to risk assessment. The experimental database on TCDD is very large; from it there are data on the nature of biological response in many organ systems, on dose-response and time course of effects; and on possible molecular mechanisms of action. As noted above, it is in this latter area that experimental toxicology can make a unique contribution to risk assessment and causal inference. The mechanisms of action of TCDD appear to involve highly specific interactions of the TCDD molecule with an endogenous protein found in many cells, including human cells (Silbergeld & Gasiewicz, 1989; Whitlock, 1990). This receptor-mediated mechanism confers both specificity and potency upon TCDD. It provides an explanation for its ability to affect gene-related events in the cell, events related to regulation of cell growth and differentiation, such that it becomes somewhat more clear as to why TCDD induces both cancer and teratogenic effects. As understanding of TCDD-induced effects on gene regulation increases, it may be possible to reevaluate the basis for quantitative risk assessment (e.g., how many events are required for altered gene expression to occur; how stable this effect may be; how it is related to organ-specific or age-specific effects) (Whitlock, 1990). At present, our knowledge does not permit us

to invoke an approach different from the general methodology and assumptions of quantitative cancer risk assessment, as noted by EPA's expert panel in 1989.

Mechanistic information about TCDD also assists risk assessment by providing a rational basis for evaluating the risks of structurally similar molecules in the dioxin/dibenzofuran family (Safe, 1985). This is of great practical importance, since it is highly unusual for persons to be exposed to TCDD alone; TCDD is usually found in mixtures containing other dioxins and dibenzofurans, for instance, in wastes from pentachlorophenol manufacture, emissions from municipal incinerators, effluent from paper pulp mills; combustion products from fires involving PCB electrical equipment (Silbergeld & Gasiewicz, 1989). Several governments have developed integrated methods of risk assessment; most of these rely upon toxicological data to relate risk to chemical structure. The assumption behind this is goodness-of-fit with the so-called dioxin receptor, the endogenous protein with which TCDD and related compounds appear to interact as an initial stage in their biological action (Whitlock, 1990). Although there may be other mechanisms of action for dioxins, dibenzofurans, and PCBs, and other factors that confer potency (as found for octachlorodibenzo-*p*-dioxin, for instance), this assumption incorporates an objective scientific approach and a method for testing its validity. Very importantly, it provides the basis for examining the experience of persons exposed to dibenzofurans in Japan and Taiwan as relevant to evaluating the observable and inferable risks of humans from TCDD.

Conclusions

This paper has reviewed the role of toxicology in discussions of causation in regulatory and tort law. For several reasons, many of which are obviously self-serving, it has become common in some legal circles to deny value to experimental research in toxicology for this purpose. This paper argues that such a denial is based upon an incorrect analysis of the information provided by toxicology and an erroneous segregation of toxicology from the rest of biomedical science. This analysis sometimes asserts that there are conflicts between toxicology and epidemiology, which is held out as the "gold standard" for causal argument. At the same time, some legal writers deny validity to epidemiology as a source of causal inference for individuals on the grounds that, as the science of events in groups of persons, epidemiology cannot be used to determine cause in an individual. More recently, there has been an argument that there are fundamental differences between humans and other species such that observations in nonhuman subjects are irrelevant to predictions of human biology. All of these arguments are scientifically bankrupt. A careful analysis of contested areas of causation reveals little or no conflict between toxicology and epidemiology, but rather significant disparities in available data (usually lack of data on humans). The rejection of group statistical data is a rejection of the fundamental basis of scientific argument. The denial of homology over evolution is a form of creationism in the courtroom, only this time cloaked in the robes of the law.

The rejection of toxicology from law and public policy jeopardizes efficient and consistent processes of decision making in public health, whose objective is disease prevention. Preventive policies in environmental and occupational health require decision making based on preclinical data. In addition, the interpretation of epidemiological data, when available, often requires integrated evaluation of toxicology in order to establish biological plausibility.

Finally, the exclusion of toxicology from tort law but its inclusion in regulatory law seems to establish inconsistent notions of causation and admissibility that will serve to undermine a rational approach to achieving controls on hazardous exposures whether they occur before or after the fact of disease.

To the scientist, rejection of valuable sources of data is anathema, given the constant uphill struggle against ignorance in understanding and preventing human disease. The tests of validity of toxicology are those that apply to all the sciences. Toxicology can and does contribute uniquely to the resolution of important public issues related to identifying and controlling risks of toxic substances in the workplace and general environment.

Note added in proof: The U.S. Court of Appeals reversed the *Paoli* decision on September 20, 1990, among other things allowing the admissibilty of toxicological evidence.

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